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10/034,451	12/28/2001	Chad A. Mirkin	01-661-A	9317

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EXAMINER	
STRZELECKA, TERESA E	

ART UNIT	PAPER NUMBER
1637	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/034,451	MIRKIN ET AL.	
	Examiner	Art Unit	
	Teresa E. Strzelecka	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 November 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *37-43,45-71,73-75 and 77-85* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *55-68* is/are allowed.

6)☒ Claim(s) *37-43,45-54,69-71,73-75 and 77-84* is/are rejected.

7)☒ Claim(s) *85* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/11/05; 9/28/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This office action is in response to an amendment filed November 23, 2005. Claims 37-43, 45-71 and 73-85 were previously pending. Applicants amended claims 82-84 and cancelled claim 76. Claims 37-43, 45-71, 73-75 and 77-85 are pending and will be examined.

2. Applicants' amendment to the specification obviated the rejection of claims 37-43, 45-71, 73-75 and 77-85 under 35 U.S.C. 112, first paragraph, written description. Applicants' arguments obviated the objection to claim 41, and cancellation of claim 76 obviated the objection to this claim. Amendments to claims 82-84 overcame the rejection of claims 82-84 under 35 U.S.C. 112, second paragraph. All other previously presented rejections are maintained for reasons given in the "Response to Arguments" below.

3. This action is made non-final because of new grounds for rejection.

Information Disclosure Statement

4. The information disclosure statement (IDS) submitted on August 11, 2005 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

5. The information disclosure statement (IDS) submitted on September 28, 2005 was filed after the mailing date of the non-final office action on August 23, 2005. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner. The references cited in the IDS will not be printed as they are duplicates of previously-cited references.

Response to Arguments

6. Applicant's arguments filed November 23, 2005 have been fully considered but they are not persuasive.

A) Regarding the priority date of the instant claims, Applicants argue that the priority Application 60/293,861, filed May 25, 2001 provides support both for the limitation of core/shell particles with mean diameters in the range of 5-150 nm and for magnetic cores. However, the only disclosure of the nanoparticle size is that of about 12 nm nanoparticles (Abstract; page 3, last paragraph; page 4) which does not provide support for the claimed range of nanoparticle sizes. As to the fact that no magnetic cores were disclosed in the provisional application, Applicants argue that

"...The provisional application also discloses and recognizes the broad utility of the claimed core/shell nanoparticle conjugates. This utility includes the tailorability of the physical properties of the core/shell nanoparticles through the use of a variety of biomolecules and nanoparticle cores that can be chosen depending on the particular desired properties, as disclosed, for example, on the last page of the specification."

The broad statement that particle properties can be tailored at will to obtain desired properties does not provide a support for a particular claimed structural feature of the particles, namely, their magnetic cores.

The claims are given the priority date of the filing date of the instant application, December 28, 2001.

B) Regarding the rejection of claims 37-41, 43, 45-54, 69-71, 73 and 75-84 under 35 U.S.C. 103(a) over Abbott et al., Mirkin et al. and Yguerabide et al., Applicants argue the following:

a) Abbott et al. teach micrometer-sized silica particles coated with polycrystalline metal films useful as synthesis supports, purification methods and assays, with micrometer size diameters and methods of using them which include size exclusion chromatography and affinity

chromatography. Applicants conclude that Abbott et al. do not teach nanoparticles with 5-150 nm size range, methods of their preparation and use.

b) The references of Mirkin et al. and Yguerabide et al. do not provide motivation to reduce the size of Abbott's particles which are used in chromatography supports, and if their size was reduced they might not function as chromatography supports.

Regarding a), Applicants conveniently omitted from their analysis of the Abbott et al. reference to the following facts about the particles described in that references, namely:

i) The particles of Abbott et al. can be of any size (col. 9, lines 63-65). Therefore, this encompasses all possible sizes, including nanoparticles. Further, the fact that one of the preferred embodiments of the size is in the micrometer region, does not exclude other embodiments from consideration.

ii) Abbott et al. specifically teach core/shell particles with metal cores and metal, for example, gold shells by teaching a multilayered material comprising a particulate substrate (= core), a metal film layered onto the substrate (= shell) and a recognition moiety attached to the metal layer (col. 4, lines 22-35). The particulate substrate may be any metal, selected according to desired properties, for example, being magnetic (col. 9, lines 55-67; col. 10, lines 1-6, 33-67; col. 11, lines 1-4). The shells are metallic, including gold, silver, platinum, palladium, nickel and copper (col. 11, lines 34-37). Therefore, Abbott et al. teach embodiments of particles with cores comprising metals and gold shells.

iii) Abbott et al. teach recognition moieties including biomolecules, such as nucleic acids (col. 12, lines 9-25; col. 16, lines 38-54; col. 19, lines 56-59), and using the nucleic acid-particle conjugates to capture or detect other nucleic acids or analytes (col. 24, lines 13-62). The particles of Abbott et al. may be used to determine the presence or quantity of an analyte in a sample by

contacting the sample with a multilayered material, forming a complex between a recognition moiety and an analyte and detecting the analyte (col. 31, lines 44-63). Therefore, detection methods of Abbott et al. are not limited to affinity chromatography or size exclusion chromatography.

Regarding b), Mirkin et al., and especially Yguerabide et al., provide a very strong motivation to have the size of the particles in the nanometer range, for their superior optical properties which provide high detection sensitivity.

The rejection is maintained.

Priority

7. Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged. However, the provisional application upon which priority is claimed fails to provide adequate support under 35 U.S.C. 112 for claims 37-43, 45-71 and 73-85 of this application. The priority application No. 60/293,861, filed May 25, 2001 does not provide support for limitations of core/shell nanoparticles with magnetic cores and mean diameter of 5 to 150 nm. Therefore, the priority date of the instant claims is the filing date of the instant application, December 28, 2001.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claim 46 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 46 is rejected based on the limitation "the gold shell ranging from about 0.5 to about 2 monolayers in thickness". It seems therefore that Applicants contemplated monolayers of fractional thickness. However, there is no support in the specification for these limitations. As evidenced by Applicants on page 12, line 3, one monolayer of Au is 0.3 nm thick, which corresponds to a diameter of a single Au atom. Therefore, it is not clear how one would make a half of a monolayer, for example, since this would require splitting the Au atom in two. Therefore, the only numbers of monolayers which are supported by the specification are one, two or three (Fig. 4).

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 46 and 78-81 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claim 46 is indefinite over the recitation of "the gold shell ranging from about 0.5 to about 2 monolayers in thickness". One monolayer of gold equals to a layer of single atoms, therefore 0.5 monolayers would require splitting Au atoms, therefore, it is not clear how such monolayers can exist.

B) Claims 78-81 are indefinite in claim 78. Claim 78 recites the limitation "the gold salt" in line1. There is insufficient antecedent basis for this limitation in the claim. Claim 69, from which claim 78 depends, does not contain the limitation of a gold salt.

Claim Rejections - 35 USC § 102

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

13. Claims 37, 38, 40-42 and 46-51 rejected under 35 U.S.C. 102(e) as being anticipated by Cheon et al. (U.S. Patent No. 6,783,569).

Regarding claims 37, 41 and 46-51, Cheon et al. teach a core/shell nanoparticle conjugate comprising:

a) a core/shell nanoparticle comprising a magnetic core and a non-alloying gold shell surrounding the core, the gold shell having a predetermined shell thickness and the core/shell nanoparticle having a mean diameter ranging from 5 to 150 nm (Cheon et al. teach non-alloying core-shell nanopaticles (Fig. 1, Fig. 13, Fig. 25) with mean diameter of 1 to 100 nm (col. 1, lines 26, 27) having a core and a shell (col. 4, lines 4-14). Cheon et al. teach magnetic cores of iron, cobalt, nickel, iron, cobalt and nickel alloys (col. 4, lines 14-48) and gold shells (col. 4, line 56).); and

(b) oligonucleotides attached to the gold shell, wherein the non-alloying gold shell is generated on a surface of the core by simultaneous addition of a solution comprising a gold salt and a solution comprising a reducing agent to a solution containing the metal-containing core (Cheon et al. teach DNA (= oligonucleotides) attached to the nanoparticles (col. 8, lines 59-64). Since Applicants did not define the term "oligonucleotide" it is interpreted as any nucleic acid of any length. The limitation of gold shell generated by a process of addition of gold salt and reducing agent to a solution containing the metal-containing core is a product-by-process limitation, therefore, it is not taken into account when comparing the product with prior art).)

Claim 41 does not add a structural limitation to claim 37, as it concerns the method of determining the thickness of a gold shell.

Regarding claim 38, Cheon et al. teach DNA (= oligonucleotides) attached to the nanoparticles (col. 8, lines 59-64). Since every DNA molecule has a sequence complementary to another DNA molecule, Cheon et al. inherently teach this limitation.

Regarding claim 40, Cheon et al. teach cores comprising Fe, Co or Ni (col. 4, lines 14-48).

Regarding claim 42, Cheon et al. teach cores comprising FePt and FeAu (col. 4, lines 33, 34).

Regarding claim 46, Cheon et al. teach cores of 4-13 nm (col. 9, lines 40-48), and core-shell nanoparticles of about 6.25 nm in diameter (Fig. 13). Therefore, if the core was 4 nm, the shell thickness is 1.25 nm, or 4 monolayers in thickness, and if the core was 6 nm, the shell is one monolayer in thickness, anticipating the limitation of "about 0.5 to about 2 monolayers in thickness".

Note regarding rejection of claims 47-51: these are product-by-process claims, and it is not clear how the method of making a product of claims 47-51 and 72 makes the final product, i.e., a core-shell nanoparticle with oligonucleotide bound to it, different from the product of Cheon et al. (see MPEP 2113). Applicants added a limitation to claim 47 of addition of gold salt and reducing agent resulting in a reaction mixture having a gold salt concentration of about 2 μm. According to the specification (page 13, lines 12-14), such concentration inhibits the formation of gold cluster nucleation sites. However, it is not clear how this affects the structure of the final product.

MPEP 2113 Product-by-Process Claims

PRODUCT-BY-PROCESS CLAIMS ARE NOT LIMITED TO THE MANIPULATIONS OF THE RECITED STEPS, ONLY THE STRUCTURE IMPLIED BY THE STEPS.

"[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from

a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985) (citations omitted) (Claim was directed to a novolac color developer. The process of making the developer was allowed. The difference between the inventive process and the prior art was the addition of metal oxide and carboxylic acid as separate ingredients instead of adding the more expensive pre-reacted metal carboxylate. The product-by-process claim was rejected because the end product, in both the prior art and the allowed process, ends up containing metal carboxylate. The fact that the metal carboxylate is not directly added, but is instead produced in-situ does not change the end product.).

Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Rejections based on the Cheon et al. reference

15. Claims 39, 43, 45, 52-54, 69-71, 73-75 and 82-84 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cheon et al. (U.S. Patent No. 6,783,569) and Mirkin et al. (U.S. Patent No. 6,361,944 B1; cited in the IDS and in the previous office action).

A) Regarding claim 37, Cheon et al. teach a core/shell nanoparticle conjugate comprising:

a) a core/shell nanoparticle comprising a magnetic core and a non-alloying gold shell surrounding the core, the gold shell having a predetermined shell thickness and the core/shell nanoparticle having a mean diameter ranging from 5 to 150 nm (Cheon et al. teach non-alloying core-shell nanopaticles (Fig. 1, Fig. 13, Fig. 25) with mean diameter of 1 to 100 nm (col. 1, lines 26, 27) having a core and a shell (col. 4, lines 4-14). Cheon et al. teach magnetic cores of iron, cobalt, nickel, iron, cobalt and nickel alloys (col. 4, lines 14-48) and gold shells (col. 4, line 56).); and

(b) oligonucleotides attached to the gold shell, wherein the non-alloying gold shell is generated on a surface of the core by simultaneous addition of a solution comprising a gold salt and a solution comprising a reducing agent to a solution containing the metal-containing core (Cheon et al. teach DNA (= oligonucleotides) attached to the nanoparticles (col. 8, lines 59-64). Since Applicants did not define the term "oligonucleotide" it is interpreted as any nucleic acid of any length. The limitation of gold shell generated by a process of addition of gold salt and reducing agent to a solution containing the metal-containing core is a product-by-process limitation, therefore, it is not taken into account when comparing the product with prior art).)

Regarding claim 69, Cheon et al. teach using the DNA-bound nanoparticles in disease diagnosis (col. 8, lines 60-64).

Regarding claim 73, Cheon et al. teach cores comprising Fe, Co or Ni (col. 4, lines 14-48).

Regarding claim 74, Cheon et al. teach cores comprising FePt and FeAu (col. 4, lines 33, 34).

B) Cheon et al. do not teach metal oxide cores, oligonucleotide densities of at least 10 picomoles/cm^2, or least 15 picomoles/cm^2, or from about 15 picomoles/cm^2 to about 40 picomoles/cm^2. Cheon et al. do not teach detection of nucleic acids bound to a surface or hybridization conducted in the presence of magnetic field.

C) Mirkin et al. teach detection of nucleic acids by hybridization using nanoparticle-oligonucleotide conjugates (Abstract).

Regarding claim 39, Mirkin et al. teach oligonucleotides attached to a gold surface using functional groups (col. 17, lines 15-67).

Regarding claims 43, 45, 75 and 77, Mirkin et al. teach nanoparticle-oligonucleotide conjugates used in nucleic acid detection methods (col. 2, lines 6-17). Mirkin et al. teach

nanoparticles being magnetic (col. 16, lines 29-32), and Fe_3O_4 core nanoparticles with a silica shell, which can be conjugated to oligonucleotides (col. 33, lines 19-27).

Regarding claims 52 and 82, Mirkin et al. teach oligonucleotide surface density of at least 10 picomoles/cm^2 (col. 49, line 24).

Regarding claims 53 and 83, Mirkin et al. teach oligonucleotide surface density of at least 15 picomoles/cm^2 (col. 49, lines 26, 27).

Regarding claims 54 and 84, Mirkin et al. teach oligonucleotide surface density of at least 15 picomoles/cm^2 to no greater than about 35-40 picomoles/cm^2 (col. 49, lines 26-32).

Regarding claims 78 and 79, Mirkin et al. teach $HAuCl_4$ (col.42, lines 58-67).

It would have been *prima facie* obvious to one of ordinary skill in the art to have used nanoparticle conjugates with oligonucleotide density of at least 10 picomoles/cm^2 or at least 15 picomoles/cm^2 to no greater than about 35-40 picomoles/cm^2 of Mirkin et al. in the conjugates of Cheon et al. The motivation to do so, provided by Mirkin et al., would have been that a surface density of between 10 and 40 picomoles/cm^2 provided stable oligonucleotide conjugates (col. 49, lines 25-32).

Regarding claim 69, Mirkin et al. teach detection of analyte DNA bound to a surface, the method comprsing:

(a) contacting the surface with a solution comprising core/shell nanoparticle oligonucleotide conjugates of claim 37, wherein the nanoparticle core is magnetic, and wherein the contacting takes place under conditions effective to allow hybridization of the core/shell nanoparticle oligonucleotide conjugates with the bound nucleic acid (Mirkin et al. teach contacting nanoparticle-oligonucleotide conjugates with analyte nucleic acid bound to a substrate (Fig. 13A; col. 2, lines 6-

17; col. 19, lines 43-50; col. 21, lines 19-59). Mirkin et al. teach nanoparticles being magnetic (col. 16, lines 29-32).);

(b) subjecting the nanoparticle conjugate to an external magnetic field so as to accelerate movement of the nanoparticle conjugate to the surface to promote interaction between the nanoparticle conjugate and the nucleic acid (Mirkin et al. teach application of magnetic field (col. 33, lines 45 and 60, 61).);

(c) removing from the surface any nanoparticle conjugates that have not hybridized with the nucleic acid (Mirkin et al. teach washing unbound nanoparticle conjugates from the substrate (col. 21, lines 60-63).); and

(d) observing a detectable change brought about by hybridization of the nucleic acid with the nanoparticle conjugates (Mirkin et al. teach observing a detectable change brought about by hybridization (col. 22, lines 22-39 and 57-65).

Regarding claim 70, Mirkin et al. teach nanoparticles being magnetic (col. 16, lines 29-32), and Fe_3O_4 core nanoparticles with a silica shell, which can be conjugated to oligonucleotides (col. 33, lines 19-27).

Regarding claim 71, Mirkin et al. teach washing unbound nanoparticle conjugates from the substrate (col. 21, lines 60-63).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have combined magnetic-core particle hybridization of Mirkin et al. with disease diagnosis of Cheon et al. The motivation to do so would have been that oligonucleotides attached to magnetic particles could be removed from solution by application of a magnetic field, allowing easy separation of hybridization products from solution.

16. Claims 37-41, 43, 45-54, 69-71, 73, 75 and 77-84 are rejected under 35 U.S.C. 103(a) as being unpatentable over Abbott et al. (U. S. Patent No. 6,277,489 B1; cited in the IDS and in the previous office action), Mirkin et al. (U.S. Patent No. 6,361,944 B1; cited in the IDS and in the previous office action) and Yguerabide et al. (Anal. Biochem., vol. 262, pp. 157-176, 1998; cited in the IDS).

> The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). For applications filed on or after November 29, 1999, this rejection might also be overcome by showing that the subject matter of the reference and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person. See MPEP § 706.02(l)(1) and § 706.02(l)(2).

A) Regarding claims 37, 41 and 47-51, Abbott et al. teach a multilayered material comprising a particulate substrate (= core), a metal film layered onto the substrate (= shell) and a recognition moiety attached to the metal layer (col. 4, lines 22-35). The particulate substrate may be any metal, selected according to desired properties, for example, being magnetic (col. 9, lines 55-67; col. 10, lines 1-6, 33-67; col. 11, lines 1-4). The particles can be of any size (col. 9, lines 63-65).

The particulate substrate is coated with a metal layer (= shell), such as gold, silver, platinum, palladium, nickel and copper, with gold being particularly preferred (col. 9, lines 3-13; col. 11, lines 34-55). An organic layer is attached to the metal layer and provides a link to the recognition moiety. The limitation of gold shell generated by a process of addition of gold salt and reducing

agent to a solution containing the metal-containing core is a product-by-process limitation, but it is taught by Abbott et al. (col. 55, lines 59-67). Further, claim 41 does not add a structural limitation to claim 37, as it concerns the method of determining the thickness of a gold shell.

Regarding claim 38, Abbott et al. teach recognition moieties including biomolecules, such as nucleic acids (col. 12, lines 9-25; col. 16, lines 38-54; col. 19, lines 56-59).

Regarding claim 39, Abbott et al. teach oligonucleotides having reactive groups which can bind to nanoparticle (col. 22, lines 66, 67; col. 23, lines 1-5).

Regarding claims 40 and 73, Abbott et al. teach metal-containing cores comprising Fe or Ni (col. 10, lines 34-36).

Regarding claims 43 and 75, Abbott et al. teach metal oxides, for example Fe_2O_3, NiO (col. 10, lines 34-36).

Regarding claim 46, Abbott et al. teach at least one layer of the metal coating (col. 11, lines 44-46).

Note regarding rejection of claims 47-51: these are product-by-process claims, and it is not clear how the method of making a product of claims 47-51 and 72 makes the final product, i.e., a core-shell nanoparticle with oligonucleotide bound to it, different from the product of Abbott et al. (see MPEP 2113). Applicants added a limitation to claim 47 of addition of gold salt and reducing agent resulting in a reaction mixture having a gold salt concentration of about 2 μm. According to the specification (page 13, lines 12-14), such concentration inhibits the formation of gold cluster nucleation sites. However, it is not clear how this affects the structure of the final product.

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PRODUCT-BY-PROCESS CLAIMS ARE NOT LIMITED TO THE MANIPULATIONS OF THE RECITED STEPS, ONLY THE STRUCTURE IMPLIED BY THE STEPS.

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Regarding claim 69, Abbott et al. teach a multilayered material comprising a particulate substrate (= core), a metal film layered onto the substrate (= shell) and a recognition moiety attached to the metal layer (col. 4, lines 22-35). The multilayered material may be used to capture a molecule in a purification process or an assay, and the captured molecule may be a nucleic acid (col. 24, lines 13-62). The multilayered material may be used to determine the presence or quantity of an analyte in a sample by contacting the sample with a multilayered material, forming a complex between a recognition moiety and an analyte and detecting the analyte (col. 31, lines 44-63).

Regarding claims 78-81, Abbott et al. teach treating the inner metal-containing nanoparticle cores simultaneously with a solution comprising a gold salt and a solution comprising a reducing agent under conditions that produce a non-alloying gold shell surrounding the nanoparticle cores (Abbott et al. teach treating the core particles with a solution containing a gold salt, such as such as $Na_3Au(SO_3)_2$ and a reducing agent (col. 37, lines 6-38).

Regarding claims 80 and 81, Abbott et al. teach sodium borohydride, $NaBH_4$ (col. 37, line 36).

B) Abbott et al. do not teach particles ranging in size from 5 to 150 nm, nanoparticle core being magnetic, but they do teach that the metal cores may any metals or may be selected for their

magnetic properties. Abbott et al. do not teach oligonucleotide densities of at least 10 picomoles/cm^2, or least 15 picomoles/cm^2, or from about 15 picomoles/cm^2 to about 40 picomoles/cm^2. Abbott et al. do not teach detection of nucleic acids bound to a surface or hybridization conducted in the presence of magnetic field.

C) Mirkin et al. teach detection of nucleic acids by hybridization using nanoparticle-oligonucleotide conjugates (Abstract).

Regarding claim 37, Mirkin et al. teach nanoparticles with sizes of 13 nm (col. 42, line 58; col. 46, line 36)

Regarding claims 45 and 77, Mirkin et al. teach nanoparticle-oligonucleotide conjugates used in nucleic acid detection methods (col. 2, lines 6-17). Mirkin et al. teach nanoparticles being magnetic (col. 16, lines 29-32), and Fe_3O_4 core nanoparticles with a silica shell, which can be conjugated to oligonucleotides (col. 33, lines 19-27).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used magnetic-core of Mirkin et al. in the nanoparticles of Abbott et al. The motivation to do so would have been that oligonucleotides attached to magnetic particles could be removed from solution by application of a magnetic field, allowing easy separation of hybridization products from solution.

Regarding claims 52 and 82, Mirkin et al. teach oligonucleotide surface density of at least 10 picomoles/cm^2 (col. 49, line 24).

Regarding claims 53 and 83, Mirkin et al. teach oligonucleotide surface density of at least 15 picomoles/cm^2 (col. 49, lines 26, 27).

Regarding claims 54 and 84, Mirkin et al. teach oligonucleotide surface density of at least 15 picomoles/cm^2 to no greater than about 35-40 picomoles/cm^2 (col. 49, lines 26-32).

Regarding claims 78 and 79, Mirkin et al. teach $HAuCl_4$ (col.42, lines 58-67).

It would have been *prima facie* obvious to one of ordinary skill in the art to have used nanoparticle conjugates with oligonucleotide density of at least 10 picomoles/cm^2 or at least 15 picomoles/cm^2 to no greater than about 35-40 picomoles/cm^2 of Mirkin et al. in the conjugates of Abbott et al. The motivation to do so, provided by Mirkin et al., would have been that a surface density of between 10 and 40 picomoles/cm^2 provided stable oligonucleotide conjugates (col. 49, lines 25-32).

Regarding claim 69, Mirkin et al. teach detection of analyte DNA bound to a surface, the method comprsing:

(a) contacting the surface with a solution comprising core/shell nanoparticle oligonucleotide conjugates of claim 37, wherein the nanoparticle core is magnetic, and wherein the contacting takes place under conditions effective to allow hybridization of the core/shell nanoparticle oligonucleotide conjugates with the bound nucleic acid (Mirkin et al. teach contacting nanoparticle-oligonucleotide conjugates with analyte nucleic acid bound to a substrate (Fig. 13A; col. 2, lines 6-17; col. 19, lines 43-50; col. 21, lines 19-59). Mirkin et al. teach nanoparticles being magnetic (col. 16, lines 29-32).);

(b) subjecting the nanoparticle conjugate to an external magnetic field so as to accelerate movement of the nanoparticle conjugate to the surface to promote interaction between the nanoparticle conjugate and the nucleic acid (Mirkin et al. teach application of magnetic field (col. 33, lines 45 and 60, 61).);

(c) removing from the surface any nanoparticle conjugates that have not hybridized with the nucleic acid (Mirkin et al. teach washing unbound nanoparticle conjugates from the substrate (col. 21, lines 60-63).); and

(d) observing a detectable change brought about by hybridization of the nucleic acid with the nanoparticle conjugates (Mirkin et al. teach observing a detectable change brought about by hybridization (col. 22, lines 22-39 and 57-65).

Regarding claim 70, Mirkin et al. teach nanoparticles being magnetic (col. 16, lines 29-32), and Fe_3O_4 core nanoparticles with a silica shell, which can be conjugated to oligonucleotides (col. 33, lines 19-27).

Regarding claim 71, Mirkin et al. teach washing unbound nanoparticle conjugates from the substrate (col. 21, lines 60-63).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have combined magnetic-core particle hybridization of Mirkin et al. with analyte detection assays of Abbott et al. The motivation to do so would have been that oligonucleotides attached to magnetic particles could be removed from solution by application of a magnetic field, allowing easy separation of hybridization products from solution.

D) Neither Abbott et al. not Mirkin et al. teach nanoparticles with average size of 5-150 nm.

E) Yguerabide et al. teach use of submicroscopic light-scattering particles as labels in clinical and biological applications (Abstract; page 164, second and fifth paragraphs). Specifically, they teach that the extinction coefficient and its absorption maximum of nanoparticles varies with their size (Fig. 3; page 166, fourth paragraph), therefore allowing for tuning of their spectral properties according to their size. These particles also exhibit strong light-scattering properties (Fig. 4). Finally, they teach that sensitivity of detection of gold particles by scattering increases with their size as estimated by a number of fluorescein molecules which produce the same signal as one gold nanoparticle (Table 1; page 168, second paragraph).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used nanoparticles of different sizes of Yguerabide et al. in the methods of DNA detection by nanopaticle-oligonucleotide conjugates of Abbott et al. and Mirkin et al. The motivation to do so, provided by Yguerabide et al., would have been that "The light-producing powers of the 87- and 118-nm particles are equivalent to more than one million fluorescein molecules.." (page 168, second paragraph), and

"...Because we can detect a single particle in the field of the microscope objective, our sensitivity is usually limited by background signal due to nonspecific binding. However, we have found that nonspecific binding can be reduced to very low levels in our gold, light-scattering immuno- and DNA probe assays by the proper use and selection of stabilizing and blocking agents. Through these agents we have been able to achieve sensitivities which are better than, for example, a comparable ELISA and the procedures are much simpler and less expensive. In actual solid-phase assays with clinical samples (including fecal samples), we have been able to achieve sensitivities of 0.001 particles/mm2 on the transparent assay surface. In high-density microarray formats, we can easily detect, by eye or with a video camera and microscope, gold particles in 20 x 20-μm assay squares, or larger squares, and achieve a wide concentration detection range. The signal from each square can be quantified by image analysis using steady state intensity or particle counting methods." (page 174, last paragraph; page 175, first paragraph).

Allowable Subject Matter

17. No references were found teaching or suggesting claims 55-68 and 85. Claims 55-68 are allowed.

18. Claim 85 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Teresa E. Strzelecka whose telephone number is (571) 272-0789. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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PATENT EXAMINER
Teresa Strzelecka
02/03/06